Review Article

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Novel technology and future prospects of ocular drug delivery

Anchal Tyagi*, Pramod Kumar Sharma, Rishabha Malviya

Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Yamuna Expressway, Greater Noida, U.P., India

Abstract: The eye is a complex organ of the body. In ocular drug delivery, advantages include ease of administration and reduced frequency of administration for better patient acceptance. Opportunities for improving drug delivery application in case of anterior ocular diseases and posterior ocular diseases should be identified. In this review, new technology such as eye sol and cyclAsol and some nutrient transporters such as amino acid transporter, vitamin C transporter, glucose transporter and intraocular implants are described. In this review, authors also mentioned marketed products and future area of investigation for improved ocular drug delivery.

Keywords: Ocular drug delivery; Eye sol; CyclAsol; Ophthalmic route

1. Introduction

The research area of ophthalmic drug delivery is very much developed and rapidly evolving. The conventional ocular drug delivery systems are suspensions, ointments and solutions. Its disadvantages are increased precorneal elimination, high variability, rapid spillage of drug, blurred vision and poor bioavailability of drug in the ocular cavity. Ophthalmic solutions are available in a single dose or multidose formulations in a wide variety of glass and plastic dropper bottles, which deliver drops with a volume between 25 and 70 µL. The normal tear production rate in humans is 1 µL/min under resting conditions.

1.1. Various challenges in poor bioavailability of drugs instilled through the eyes

Difficulties in delivering drugs through the ophthalmic route have many challenges, particularly, the drug delivery into anterior and posterior segments. In the eye, topical drug formulations are eye drops, suspensions, gel and ointments. They are delivered to the anterior segment of the eye and have ease of administration [1]. Local drug administration to the anterior segment of the eye with topical application is significantly limited by the clearance mechanisms which include solution drainage, tear turnover, lachrymation, transient residence time in the cul-de-sac, binding by the lachrymal proteins, relative impermeability of the corneal epithelial membrane and non-productive absorption [2-8].

1.2. Limitations

In the ocular drug delivery, some limitations are strength of gel, physical state and phase transition.

Strength of gel: The shear force in cul-de-sac so gel should be strong at the prolonged residence time of drug [9]. ***Physical state***: Formulation is liquid and it should be free flowing, which allows ease of administration with reproducible dose delivery [10]. ***Phase transition***: When the formulation is liquid in form, then after the instillation, it should change in gel form (sol-to-gel) is called a phase transition [11].

The eye dosage forms are administered directly for localized therapy [12]. In the eye, the Food and Drug Administration (FDA) [13] have approved few veterinary drugs (e.g. topical antibiotics, corticosteroids, and cyclosporine) for marketing. The eye is highly sensitive; it offers unique locations for delivery system placement. Complications in ocular drug delivery are mentioned in Fig 1. The strategies for ocular drug delivery are classified as noninvasive topical strategies and invasive implant technologies.

1.3. Noninvasive topical strategies

Topical ophthalmic solutions are sufficient to elicit an efficacy response to the ocular surface. In this effect those factors include the concentration instilled dose into the eye, conjunctival clearance, and hydraulic conductivity of the ocular tissues and intraocular tissue. To improve the drug levels two approaches are used a) Increasing topical residence time b) Increasing drug permeation through tissue. Topical residence time can be increased using gels and solid inserts. Drug permeation can be extended using appropriate pro-drugs, solubilization vehicles or iontophoretic methods.

*Corresponding author; E-mail: tyagianchal1234@gmail.com, rishabhamalviya19@gmail.com; Tel: +91-9716504887

1.3.1. Gel Technologies

The gel formulations have increased topical concentrations for enhanced therapy of surface diseases and enhance the drug levels in posterior eye. The expectations for performance of gels should be appropriate with the considerate gels are predominantly water and open pore structure. They do not confer extension of drug duration much beyond a few hours.

1.3.2. Nanoparticle technologies

In the form of highly hydrophobic drug, eye can easily tolerate for 1-5 micron sized particle for the administration. Nanoparticles offer two advantages in ophthalmic drug delivery. They are: (i) Drug surface area is increased per mole of drug compound and increases absorption and tissue exposure; (ii) The nanoparticles of drug are modified to contain a targeting mechanism to identification by tissue receptors for interfering RNA uptake.

Microneedles: Microneedles enhance drug delivery to the eye. Two types of microneedles are used in ocular drug delivery such as: 1) solid microneedles and 2) hollow microneedles. Solid microneedles are coated with Pilocarpine or fluorescein and injected into the cornea. Hollow microneedles were used to deliver 10–35 µL of fluid into the sclera [14].

1.3.3. Invasive implant technologies

Ocular implants have the ability to directly deliver the drug at constant therapeutic levels to the specific site of ocular disease and decrease the systemic side effects. Biodegradable implants are able to mold themselves into various shapes and they do not require removal. The advantages of Nonbiodegradable implants are steady, controlled release of a drug for potentially long periods of time. Biodegradable inserts are placed in the lower conjunctival sac for sustained release of drugs.

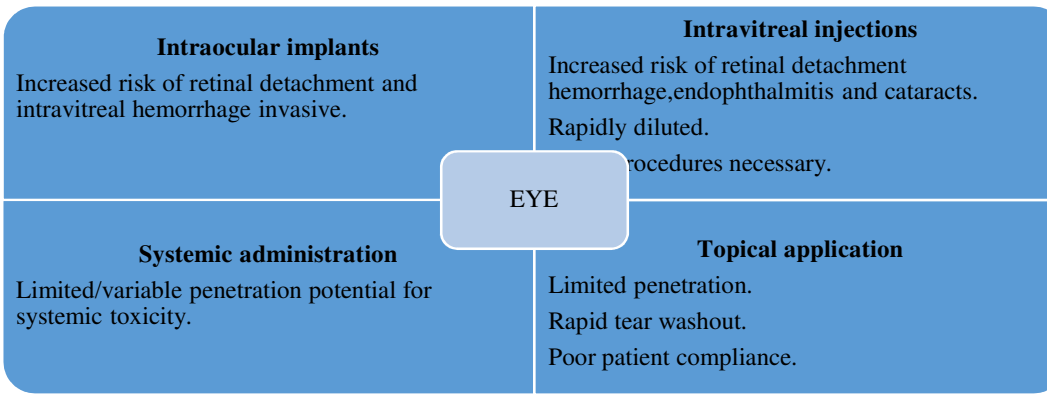

Fig 1. Complications in ocular drug delivery [15]

1.4. Opthalmic inserts

Ophthalmic inserts are sterile preparations with a solid or a semisolid. Inserts are increasing the contact time between the conjunctival tissue and preparation to ensure sustained release for topical treatment [16]. The inserts are placed in the lower fornix of the eye or on the cornea. Ocular inserts advantages are increasing the patient compliance by decrease the dosing frequency. Classification of ocular inserts is mentioned in Fig 2.

1.5. Role of Penetration Enhancers in Ocular Drug Delivery

The penetration of drugs has been modified with the help of penetration enhancers through the barriers of the cornea and epithelial layer [18]. In ocular formulation, penetration enhancers are used such as - ethylenediaminetetraacetic acid (EDTA), saponins, glychocholate, cyclodextrin, brij35, dimethylsulphoxide (DMSO), tween20 and bile salts etc. Cyclodextrin is both hydrophilic and lipophilic in nature and it enhances the stability, water solubility and absorption of drug and decrease the ocular irritation. Cyclodextrin (2HP-β-CD) enhanced the concentration of dexamethasone and the permeability of ocular drug [19]. In the form of penetration enhancer benzalkonium chloride is used in transscleral delivery of betamethasone phosphate and enhance the concentration and permeation of drug in the choroid and retina [20]. The bioavailability of drugs are improved with absorption enhancer but concentration of drug is affecting the toxic level of ocular formulation. The concentration of penetration enhancers is damaging the corneal membrane. This ophthalmic preparation shows the high enhancing effect and low irritation. It also causes poor tolerance and ocular damaging.

In ocular drug delivery, eye drops are used for inefficient delivery system, because eye drops range from 20-50 µL in volume, but the precorneal space in healthy volunteers is only 7 µL. The rapid turnover of precorneal tear and aqueous humor, the ocular residence time for most drugs is relatively short. In ocular therapy, different drug delivery systems are used as mentioned in Fig 3.

1.6. Challenges and barriers in ocular drug delivery

In ocular drug delivery, major barriers are physiochemical properties of the drug, non-corneal absorption, corneal barrier, and elimination of lacrimal

fluid. The rate of penetration in the cornea is affected such as molecular size, solubility, molecular shape and degree of ionization and lipophilicity. The volume of liquid dosage forms such as suspensions and the solution is drained into nasolachrymal duct and clean the precorneal area resulting in poor bioavailability [22]. In the corneal barrier, few administered drugs are reaching into intraocular tissue and corneal epithelium and protecting the invasion of foreign molecules. When the hydrophilic corneal stroma is a rate-limiting barrier to ocular absorption [23, 24]. Ophthalmic drug delivery challenges and barriers are:

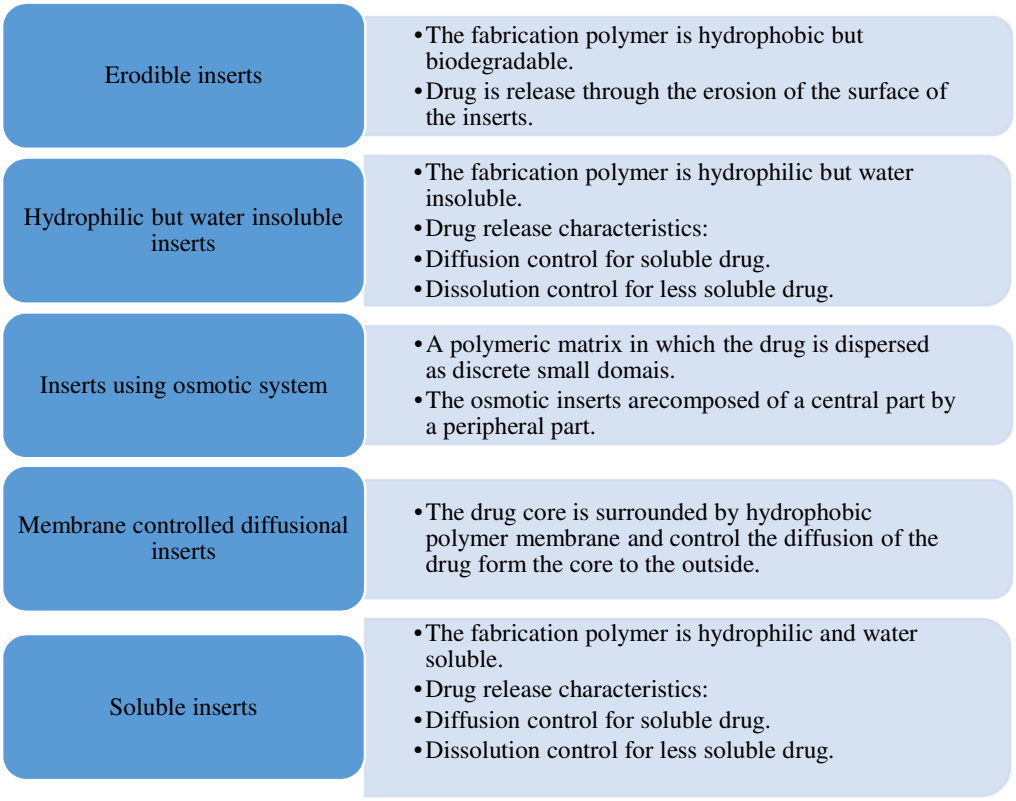

Fig 2. Classification of ophthalmic inserts [17]

Lacrimal fluid-eye barriers: The epithelial cells corneal barrier is formed upon maturation. The limbal region moves towards the center of the cornea and apical surface. The apical corneal epithelial cells are closely constrained to the limit of drug permeation [25]. The hydrophilic drug permeability in the cornea is less as compared to the lipophilic drugs [26]. The route of absorption is greater for bioorganic compounds such as peptides and proteins. The cornea is less leaky epithelium as compared to the conjunctiva. The cornea surface area is 20 times less than the conjunctiva [27, 28].

Drug loss from the ocular surface: The lacrimal fluid is easily removed from the surface of the eye by nasolacrimal duct. In the systemic circulation drug absorption decreases the drug concentration in lacrimal fluid. The systemic absorption occurs directly from the conjunctival sac by local

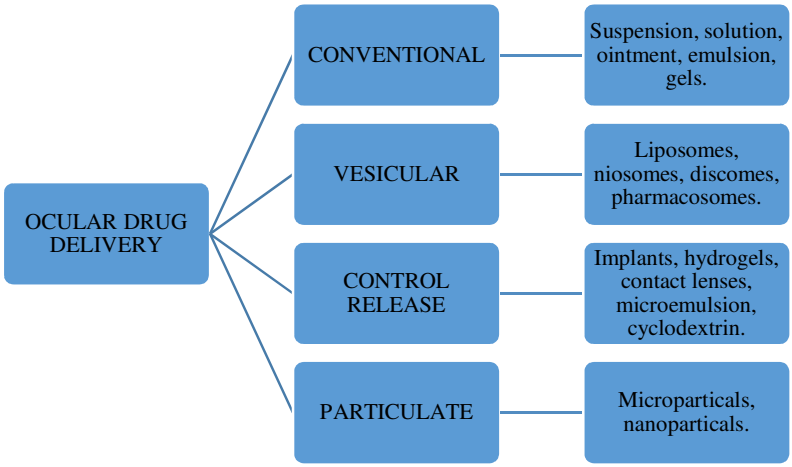

Fig 3. Different Drug Delivery Systems for Ocular Therapy [21]

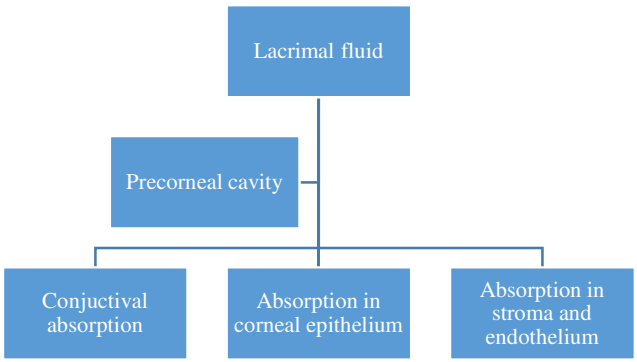

Fig 4. The drug absorption of topical ocular application [52]

blood capillaries and from the solution spilled into nasal cavity [29, 30].

Blood-ocular barriers: Blood ocular barriers protect the eye from the xenobiotics in the blood stream. Blood ocular barriers are divided into two parts: blood-aqueous barrier and blood-retinal barrier. The blood-aqueous barrier is protecting the anterior segment of the eye [31]. The blood-retinal barrier is composed of two cells in the posterior segment of the eye. The anterior blood eye barrier prevents the excess amount of plasma albumin into the aqueous humor. The posterior eye barrier between eye and blood stream consists of retinal pigment epithelium (RPE) and the compact walls of retinal capillaries [32]. These barriers have not been distinguished to possess metabolic enzyme expression and drug transporters.

Patient-Driven Challenges: The biopharmaceutical and anatomical barriers are facing the ocular delivery challenges. Instillation of eye drops is very easy and controlling eyelid movements facilitates entry of drop into the eye [33, 34]. Ocular drug delivery eye drops have major challenges to the patient because they require lifelong medication on a daily basis.

Biopharmaceutical Driven Challenges: The biopharmaceutical system contains both a lipophilic and hydrophilic component. The lipophilic biopharmaceutical system easily penetrates through the corneal endothelium and epithelium due to their high concentration of cellular membranes [35, 36]. The hydrophilic biopharmaceutical compounds more easily permeate through the sclera and the aqueous stroma [37]. The amphiphilic biopharmaceutical systems easily penetrate through the conjunctiva and cornea [38]. The biopharmaceutical delivery system and molecular mass are also affect the targeted tissue delivery [39]. The large macromolecules are penetrating the conjunctiva and the endothelium and small macromolecules are better penetrate to the corneal epithelium, sclera and stroma [40, 41].

Anatomical Challenges: The largest challenges to ocular drug delivery is the anatomy of the eye. The tear film also acts as a barrier against biopharmaceutical absorption. The corneal epithelium protects the tear film against pathogens and foreign substances. The mucin forms a hydrophilic layer and removes the bacteria and pathogens for ocular biopharmaceutical formulation from the surface of the eye [42]. The epithelium provides the diffusion in the presence of tight junctions at the surface.

1.7. Nutrient transporters in the eye

Epithelial cells are shown to have the nutrient transporters and receptors on their membrane surface. The various nutrient transporters are present across the cell membrane [43]. The various transporters targeted ligands enhances ocular bioavailability significantly. So many nutrients are transported through the ocular route.

1.8. Vitamin C transporter

Vitamin C or ascorbic acid protects the cornea and other ocular tissues from UV radiations. It is acting as an antioxidant and the main source of ascorbic acid is aqueous humor for cornea and lens [44]. Two specific transporters of vitamin C were identified in the ocular tissues of the human, rabbit and rat is SVCT-1 and SVCT-2. The ascorbic acid across the cells by two different transporter families [44].

1.9. Amino acid transporter

Protein synthesis or structural and functional integrity of the conjunctiva and retina/RPE amino acid are responsible. The presence of amino acid transporters on the cornea has been confirmed by gene expression and on the basis of their sodium dependency and substrate specificity [45]. The amino acid transport systems have been characterized on corneal epithelium and endothelium [46]. This transporter belongs to the neurotransmitter gene family and have the affinity for the transport of prodrugs, like Valine-ACV and Valine-GCV. The ocular drug delivery is enhancing the target of this transporter [47].

1.10. Glucose transporter

Glucose is utilized by the retina to meet the energy need of oxidative metabolism [48]. The higher metabolic rate is considered as normal for the retina. Glucose is transported across the blood-retinal and blood-aqueous barriers by a stereo-specific transporter. Glucose transporters are expressed in various forms such as GLUT1, GLUT2, GLUT3, GLUT4, GLUT5, GLUT6 and GLUT7. High-affinity glucose transporters are GLUT1, GLUT3, and GLUT4 and low affinity glucose transporters are GLUT2 and high-affinity fructose transporter are GLUT5. GLUT7 is also a low-affinity glucose transporter, but only expressed in endoplasmic reticulum [49]. Compared to any other

nutrient transporters, glucose transporters are more efficient and have more capacity.

1.11. Intraocular implants

Implants have been widely used to extend the release in ocular fluids and tissues in the posterior segment. Implants are classified into two categories based on their degradation property as - (1) Biodegradable implants and (2) Non-biodegradable implants. The implants delivery rate is variable depending upon polymer composition [50]. Implants can be in the form of solid, semi-solid based delivery systems. In the treatment of both anterior and posterior segments of the eye, implants are used. The anterior segment diseases like glaucoma filtering surgery and posterior segment diseases like proliferative vitreoretinopathy, CMV retinitis, endophthalmitis, and posterior capsule opacification, implants are used. Polyerthoesters (POE) are providing zero order release kinetics and it is hydrophobic in nature and usually degrades by surface erosion [51]. The drug absorption of the topical ocular application is mentioned in Fig 4.

1.12. Mechanism of ocular absorption

The mechanism of ocular absorption can be summarized as follows:

Corneal absorption: It is also divided in two parts as follows: *Outer epithelium:* Rate limiting barrier, with pore size 60Å, only have access to small ionic and lipophilic molecules [53]. *Transcellular transport:* Transport between corneal epithelium and stroma. *Non-corneal absorption:* Non-corneal absorption are - Penetration across sclera and conjunctiva into intra ocular tissues. Nonproductive because penetrated drug is absorbed by general circulation.

2. Future Prospect to Improve Absorption of Topical Drops

2.1. Focus on initial concepts

The drug delivery in established drug products is expedient. When the ophthalmology is advancing over the next five years, excellent compounds are to be developed for drug delivery, for example, in glaucoma [54]. In targeted drug delivery, nanotechnology is also being applied to the field of ophthalmology. Particles are trapped in the surface of the mucus layer in the tear film so tear film are cleared away with blinking approximately every second [55]. This protective mechanism also creates a therapeutic efficacy of topical ocular drugs.

In the conventional formulation for non-coated particle, when the non-coated particles adhere to the mucins and cleared with the tears via blinking [56].

Mucus penetrates particles (MPPs): Mucus particles diffuse through the tear and membrane bind mucins to the ocular surface [57].

The treatment of eye diseases and disorders is depending on the nature and extent of the disease or disorder. Diseases such as age-related macular degeneration (AMD) and diabetic retinopathy are associated with tissues at the back of the eye (BOTE) and the methods used for ocular drug delivery are for the front of the eye (FOTE). The invasive approaches to drug delivery method for delivering a drug are not useful to FOTE eye tissue that may be useful for treating BOTE diseases and disorders is iontophoresis [58]. The ocular sustained-release and other drug delivery systems are particularly to the posterior segment and significant market opportunities are [59]:

- Polymer-drug conjugate for neovascular AMD (Age related Macular Degeneration) and glaucoma.
- Microsphere and nanosphere systems for neovascular AMD and Glaucoma.
- Encapsulated cell technology with the extracellular delivery of ciliary neurotrophic factor for retinitis pigmentosa and geographic atrophy.
- Cell based programs, including stem cells for neovascular AMD.
- Preclinical novel adeno-associated viral variant technology for long-term protein delivery to the eye in DME, neovascular AMD, glaucoma and other conditions.
- Latanoprost delivery system (L-PPDS) in subjects with ocular hypertension and open angle glaucoma.
- Injectable drug delivery implant for glaucoma.
- Proprietary hydrogel technology.
- Suprachoroidal injectable suspension with triamcinolone acetonide for uveitis.
- Topical peptides for neovascular AMD and corneal injuries.
- Topical semi-fluorinated alkane delivery, enhancing drug solubility, posterior and anterior applications.
- Topical anterior mucosal delivery of posterior treatment.

The PEG medical device is compatible with a drug, provide therapeutics range from days to months. There are device technologies in research that, pending regulatory approval, stand to be game-changers in delivering less taxing, more effective options for the increasing number of ophthalmic disease patients. These technologies aim indications of diseases such as back-of-the-eye (BOTE) disorders, as well as ophthalmic diseases such as dry eye, glaucoma and cataracts that are growing disease areas in need of improved drug and device therapies. Ocular films are made of materials that are fitted over the cornea or applied to the eye in an otherwise more sustainable form, much like a contact lens or controlled-release solution. Then, they dissolve slowly enough to provide a sustained drug release and increasing the duration window for efficacy.

3. New Technology and Approaches for Ocular Drug Delivery

3.1. Eye Sol

Eye Sol is a novel topical ocular drug delivery system for poorly soluble drugs. The most accessible organs of the body are anterior segment and the drug delivery to the eye tissues is particularly problematic. This is reacted by the poor bioavailability of topical ocular drug formulations of 5% or less. Approximately 40 to 50 μL standard drop of water is activated and blinking which washes away for most

of any topically administered dose within 15 to 30 seconds after instillation.

New chemical entities (NCEs) up to 75% are considered poorly soluble, even for oral administration. Three major issues are considered for ocular formulations: safety, bioavailability, and stability. Eye sol for ocular drug delivery technology is to fulfill these requirements. SFAs are a special class of fluorocarbon compounds that have been used for more than 10 years in the posterior segment in thousands of patients with an excellent safety [60]. SFAs increase the bioavailability of drugs.

The water refractive index is similar to semi fluorinated alkanes (SFAs), so these formulations will not impair patient's vision like emulsions and oily drops. SFAs are an amphiphilic in nature, so they dissolve a number of therapeutically relevant and poorly-water-soluble compounds such as cyclosporine A and Tacrolimus [61]. In this delivery system, aqueous-free environment is increasing drug's stability by preventing oxidation and hydrolysis.

3.2. CyclASol

CyclASol is a preservative-free, clear cyclosporine solution for the treatment of dry eye disease. Semi fluorinated alkanes (SFAs) product is based on the Eye Sol technology and provided free preservative in multidose units. It is created to blur patient's vision in the absence of surfactants and irritating preservatives and improved tolerability and convenience.

Table 1. List of marketed formulations

S. No.	Name of brand	Drug	Manufacturer
1.	Dichol	Carbachol	Dahlgren
2.	Timolol Xe	Timolol maleate	Valeant Pharmaceutical
3.	Restasis	Cyclosporine	Allergan
4.	Pred forte	Prednisolone acetate	Allergan
5.	Refresh tears	Hydroxypropyl methylcellulose (HPMC)	Allergan
6.	Acivir eye	Acyclovir	Cipla
7.	Viscotear	Corbomer	Alcon Inc.

4. Conclusion

The conventional dosing is restricted to the eye. In the eye, topical drug administration (suspensions, ointments, and gels) of drug delivery occurs to the anterior segment of the eye. The limitation of ocular drug delivery is the strength of the gel, physical state, and phase transition. In the eye, few veterinary drugs have been approved for marketing by the Food and Drug Administration (FDA). In the conventional formulation, the non-coated particles adhere to the mucins with the tears via blinking and mucin particles diffuse through the tear and membrane bound mucins to the ocular surface. It can be concluded from the manuscript that some novel approaches/ technology are in need for ocular delivery of drug with great patient compliance.

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